REMARKS

Claims 15-20 are pending following entry of the above amendment. The amendment to claim 15 finds support in the specification at page 8, lines 34-35 and at page 9, lines 9-11.

A "marked-up" copy of the amended claim is appended to this Amendment.

Applicants also submit herewith a Petition under 37 C.F.R. 1.48 (b) to delete Suad Efendic and Mark Gutniak as named inventors of the present application. Thus, the sole inventor of the present application is Ole Kirk.

REJECTION OF THE CLAIMS UNDER 35 USC §103(a)

The Examiner rejected claims 15-20 as unpatentable over Buckley et al. (WO 91/11457) and Gutniak et al (Diabetologia, 33 Suppl. A73, Abstract 246, 1990) in view of Ramachandran et al. (Diabete Metabolisme 13(2):140-141, 1987), Del Prato et al (The American Journal of Medicine) and Parker et al. (Diabetes 40:Supp. 1, Abstract 847).

Buckley, Parker and Ramachandran were previously cited by the Examiner as teaching analogs and derivatives of GLP-1 useful in the treatment of diabetes (Buckley); that the combination of GLP-1 (7-37) and glibenclamide had an additive effect on the amount of insulin secreted from HIT cells in vivo (Parker); and that the combination of glibenclamide and metformin is effective in the treatment of diabetes (Ramachandran).

The newly cited Gutniak and Del Prato references are cited as teaching that the insulinotropic effect of GLP-1 is reproducible in vivo (Gutniak) and that type II diabetes is a heterogenous disorder characterized by relative insulin deficiency and impaired insulin action (Del Prato).

The Examiner therefore concludes:

"It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the GLP-1 peptides, 7-34, 7-35, 7-36 and 7-37 and analogs thereof as taught by Buckley et al and Gutniak et al with the oral hypoglycemic agents such as glibenclamide and metformin of Ramachandran et al to treat Type II diabetes because Parker et al teach that the GLP-I and glibenclamide when combined had an additive effect on the amount of insulin secretion and therefore the combination of the agents would be reasonably expected to be useful in the treatment of Type II diabetes.

One would have been further motivated to combine the GLP-1 with metformin and glibenclamide because Del Prato teach that Type II diabetes is a heterogenous disorder characterized by relative insulin deficiency and impaired insulin action and the combination of GLP-1 with the oral hypoglycemic agents would be reasonably expected to further increase

the endogenous insulin levels and therefore be useful in the treatment of Type II diabetes and further, one skilled in the art would have a reasonable expectation of success because Gutniak et al that demonstrates that the *in vitro* pharmacology of GLP-1 correlates with the *in vivo* actions" pages 3-4 of Office Action).

Applicants respectfully traverse this rejection.

In the present Office Action, the Examiner asserts that one would have been motivated to combine the GLP-1 peptides of Buckley and Gutniak with the oral hypoglycemic agents of Ramachandran (glibenclamide and metformin) with a reasonable expectation that such a combination would be useful in the treatment of type II diabetes because 1) Parker teaches that GLP-1 and glibenclamide when combined had an additive effect on the amount of insulin secretion; 2) Del Prato teaches that type II diabetes is a heterogenous disorder characterized by relative insulin deficiency and impaired insulin action; and 3) Gutniak demonstrates that the in vitro pharmacology of GLP-1 correlates with its in vivo actions.

With all due respect, Applicants disagree.

First, Applicants submit that the Examiner's characterization of the Parker reference is incorrect.

Parker does not teach that the combination of GLP-1 (7-37) and glibenclamide had an additive effect on the amount of insulin secreted from HIT cells in vivo. Rather, Parker describes experiments conducted on HIT or islet cells in vitro to determine whether or not GLP-1 and glibenclamide operate by the same mechanism or a different mechanism. Parker thus discloses nothing about combining GLP-1 and glibenclamide in vivo for treating type II diabetes.

Moreover, as Parker was an in vitro study and the experiments were not designed for the purpose of investigating therapeutic potential, Parker would not provide any motivation to combine GLP-1 and glibenclamide for treating type II diabetes.

Turning to Del Prato, as the Examiner indicates, this reference does disclose that type II diabetes is a heterogenous disorder characterized by relative insulin deficiency and impaired insulin action (first paragraph of right-hand column of page 77S). However, what Del Prato teaches as useful in the treatment of type II diabetes is "the combination of oral agents with insulin therapy" (Abstract, emphasis added) and the only such combination disclosed in Del Prato is that of insulin with a sulfonylurea; Del Prato is completely silent with respect to either component of the presently claimed combination, GLP-1 or metformin. Moreover, as

indicated in the cited Gutniak reference ("GLIP was given as an infusion"), GLP-1 was not considered by those skilled in the art in 1992 to be an oral agent (ie an agent administered orally). In this regard, Applicants note that the amended claims recite that the GLP-1 related peptide is to be administered via injection or infusion.

Finally, regarding Gutniak, Applicants do not dispute the Examiner's assertion that Gutniak demonstrates that the insulinotropic effect of GLP-1 is reproducible in vivo. Indeed, in the Background of Invention section of the present application, Applicants acknowledge that this property of GLP-1 was known in the prior art (see page 3, lines 27-30).

Thus, the three references relied on by the Examiner (Parker, Del Prato and Gutniak) as providing 1) the motivation to combine GLP-1 with metformin and 2) the reasonable expectation that such a combination would be useful in the treatment of type 2 diabetes disclose:

1) **nothing** about the combination of GLP-1 with any oral hypoglycemic agent, including a sulfonylurea such as glibenclamide, in the treatment of type 2 diabetes (see above discussion of Parker);
2) that the combination of insulin with a sulfonylurea may be useful in the treatment of type II diabetes (Del Prato); and
3) that GLP-1 administered via infusion stimulated insulin release in type 2 diabetics (Gutniak).

Given the above disclosures of the cited Parker, Del Prato and Gutniak references, Applicants fail to see how one skilled in the art reading these references would, **in the absence of impermissible hindsight analysis**, have been motivated to combine the GLP-1 peptides of Buckley or Gutniak with the oral hypoglycemic agents of Ramachandran (glibenclamide and metformin) with a reasonable expectation of success that such a combination would be useful in the treatment of type II diabetes.

Indeed, it is Applicants' position that as of the 1992 priority filing date of the present application, there was a complete absence of any suggestion in the cited prior art to use GLP-1 in combination with any oral hypoglycemic agent for the treatment of diabetes yet alone to combine metformin and GLP-1 in the treatment of type II diabetes as is presently claimed and that the Examiner in the present application is relying on impermissible hindsight

analysis to pick and choose among the oral agents known at the time of filing of the present application to be useful in the treatment of diabetes to arrive at the claimed combination.

In this regard, Applicants note that numerous oral agents other than metformin such as thiazolidinediones, the non-sulfonylurea insulin-releasing drug N-[(trans-4-isopropylcyclohexyl)-carbonyl]-D-phenylalanine (A-4166), glucosidase inhibitors (acarbose), glucagon antagonists, potasium channel openers, hepatic enzyme inhibitors, glucose uptake modulators, compounds modifying the lipid metabolism (fibrins, statins), compounds lowering food intake, and agents acting on the ATP-dependent potassium channel of the ß-cells [see, for example, Sohda et al (1992) J.Med.Chem., 35:2617-2626, which discloses thiazolidinediones; and Sato et al (1991) Diabetes Res. Clin. Pract., 12:53-59, which discloses the non-sulfonylurea insulin-releasing drug N-[(trans-4-isopropylcyclohexyl)-carbonyl]-D-phenylalanine (A-4166), copies previously provided to the PTO with the August 6, 2002 Amendment], were known as of the priority filing date of the present application to be available for the claimed treatment method.

Moreover, if the combination of GLP-1 and metformin for the treatment of type II diabetes was allegedly so obvious to one of ordinary skill in the art, Applicants raise the question of why no one prior to the present inventors suggested this combination despite the fact that the use of metformin in the treatment of diabetes dates to 35 years before the 1992 priority filing date of the present application (see last paragraph of page 33 of the Campbell reference cited by the Examiner in the February 6, 2002 Office Action) and the use of GLP-1 to at least 5 years [see Kreymann et al (1987) Lancet II: 1300-1304; copy submitted with the August 6, 2002 Amendment] before the priority filing date.

The clear answer to this question is that the combination of GLP-1 and metformin for the treatment of type II diabetes was not obvious to one of ordinary skill in the art prior to the present invention because the cited art, for the reasons set forth above, provided neither the teaching or suggestion to combine GLP-1 and metformin nor the reasonable expectation of success that such a combination would be useful in the treatment of type II diabetes.

Finally, even assuming arguendo that, as the Examiner asserts, Parker "broadly teaches (which Applicants dispute, see above arguments regarding the cited art and Parker in particular) the combination of GLP-1 peptides and oral hypoglycemic agents to increase insulin secretion" (page 3 of Office Action), Applicants submit that such an alleged teaching would not lead one to the presently claimed combination of GLP-1 peptides and metformin

because from a mechanistic point of view, such a combination would not have been obvious to one of skill in the art as of the 1992 priority filing date of the present application since GLP-1 and metformin were known to have overlapping mechanisms of action. In particular, while metformin lowers glucose by increasing insulin sensitivity in peripheral tissues, it also acts by inhibiting hepatic glucose production [see last full paragraph of page 491 of Garber et al, Am. J. Med. 103: 491-497 (1997), previously submitted in the IDS filed August 6, 2002 and citing to publications from 1992 and earlier] and GLP-1, in addition to stimulating insulin secretion, was known to decrease hepatic glucose output via its ability to inhibit glucagon secretion [see abtract of Orskov et al Endocrinology 123: 2009-2013 (1988), copy attached]. Thus, GLP-1, like metformin, shared the common property of inhibiting hepatic glucose production. By comparison, as disclosed in the aforementioned Garber reference, what one skilled in the art looked for in combining drugs for the treatment of diabetes was to combine drugs that have complementary, not overlapping, mechanisms of action. ["In view of these complementary mechanisms of action for biguanides as compared with sulfonylureas, it is understandable that metformin has synergistic action with sulfonylureas" (last full paragraph of page 491 of Garber, emphasis added)]. In addition, Applicants note that the combination of metformin and sulfonylureas taught by Garber and by the pre-1992 Ramachandran reference cited by the Examiner provides evidence that as of the 1992 priority filing date of the present application, combination therapy for diabetes using drugs other than insulin utilized oral drugs and as stated above in the discussion of Del Prato and as recited in the amended claims, GLP-1 was considered an injectable drug.

Accordingly, in view of the above arguments, Applicants respectfully submit that the combination of GLP-1 peptides and metformin recited in the pending claims is nonobvious over the cited art and withdrawal of the present rejection is respectfully requested.

In sum, in view of the above remarks, it is respectfully submitted that all claims are in condition for allowance.

Early action to that end is respectfully requested.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: May 5, 2003

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PATENT TRADEMARK OFFICE

"MARKED-UP" COPY OF THE AMENDED CLAIMS

15. (Amended) A method for treating type 2 diabetes, said method comprising administering to a patient in need of said treatment i) an effective amount of metformin via oral administration and ii) an effective amount of a GLP-1 related peptide via injection or infusion, where said GLP-1 related peptide is GLP-1 (7-37), GLP-1 (7-36) amide, an analogue of GLP-1 (7-37) or GLP-1 (7-36) amide, or a functional derivative thereof.